

CLAIMS

1. Use of a FADS2 interacting molecule for the preparation of a pharmaceutical composition for the treatment of neurogenerative diseases.
2. The use of claim 1, wherein the FADS2-interacting molecule is a FADS2 inhibitor.
3. The use of claim 2, wherein the inhibitor is selected from the group consisting of antibodies, antisense oligonucleotides, siRNA, low molecular weight molecules (LMWs), binding peptides, aptamers, ribozymes.
4. The use of any of claims 1 to 3, wherein FADS2 is part of a protein complex comprising at least one further protein selected from the proteins in table 1, third column.
5. The use of any of claims 1 to 4, wherein the interacting molecule or inhibitor modulates the activity of gamma secretase and/or beta secretase.
6. The use of any of claims 1 to 5, wherein the neurodegenerative disease is Alzheimer's disease
7. A method for identifying a gamma secretase and/or a beta secretase modulator, comprising the following steps:
 - a. identifying of a FADS2-interacting molecule by determining whether a given test compound is a FADS2-interacting molecule,
 - b. determining whether the FADS2-interacting molecule of step a) is capable of modulating gamma secretase and/or beta secretase activity.

8. The method of claim 7, wherein in step a) the test compound is brought into contact with FADS2 and the interaction of FADS2 with the test compound is determined.
- 5
9. The method of claim 8, wherein the interaction of the test compound with FADS2 results in an inhibition of FADS2 activity.
10. The method of any of claims 7 to 9, wherein in step b) the ability of the gamma secretase and/or the beta secretase to cleave APP is measured.
- 10
11. A method for preparing a pharmaceutical composition for the treatment of neurodegenerative diseases, comprising the following steps:
- 15
- a. identifying a gamma secretase and/or beta secretase modulator according to claims 7 to 11, and
- b. formulating the gamma secretase and/or beta secretase modulator to a pharmaceutical composition.
- 20
12. A protein complex comprising
- a) FADS2 and
- 25
- b) either one or more proteins of the Nicastrin (a) complex, of the Nicastrin (b) complex, of the Nicastrin (c) complex, of the BACE1-complex (a), of the BACE1-complex (b), of the Psen2-complex or of the PTK7 complex.
- 30
13. The complex of claim 5, wherein the one or more proteins of the Nicastrin (a) complex are selected from the group consisting of
- (i) "18 kDa microsomal signal peptidase subunit" (SEQ ID No:53)

- (ii) "25 kDa microsomal signal peptidase subunit " (SEQ ID No:119)
(iii) "ATP-binding cassette, sub-family A, member 3" (SEQ ID No:103),
(iv) "Aph-1a" (SEQ ID No:1),
5 (v) "BACE1" (SEQ ID No:68),
(vi) "BSCv protein" (SEQ ID No:70),
(vii) "CGI-13" (SEQ ID No:72)
(viii) "Casein kinase II beta chain " (SEQ ID No:74),
(ix) "Cathepsin B" (SEQ ID No:75),
10 (x) "ENSG00000144840" (SEQ ID No:79).
(xi) "FLJ13977" (SEQ ID No:81),
(xii) "FLJ20342" (SEQ ID No:56),
(xiii) "FLJ20481" (SEQ ID No:82),
(xiv) "FLJ22390" (SEQ ID No:84),
15 (xv) "Hypothetical protein tyrosine phosphatase ensg00000149185 " (SEQ ID No:86),
(xvi) "ICAM-2" (SEQ ID No:87)
(xvii) "KIAA1181" (SEQ ID No:88),
(xiii) "KIAA1533" (SEQ ID No:89),
20 (xix) "Mesenchymal stem cell protein DSCD75 " (SEQ ID No:91)
(xx) "NICE-3" (SEQ ID No:58),
(xxi) "Neurotrypsin" (SEQ ID No:92),
(xxii) "Nicastrin" (SEQ ID No:9),
(xxiii) "PP1, regulatory subunit 15B " (SEQ ID No:93)
25 (xxiv) "Pen-2" (SEQ ID No:10)
(xxv) "Presenilin-1" (SEQ ID No:14),
(xxvi) "Presenilin-2" (SEQ ID No:66),
(xxvii) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:94)
(xxviii) "Protein similar to stromal cell-derived factor 2 " (SEQ ID No:95)
30 (xxix) "Protocadherin beta 8 " (SEQ ID No:96)
(xxx) "REP8 protein " (SEQ ID No:97)
(xxxi) "RING finger protein 5 " (SEQ ID No:98)

(xxxii) "Retinal short-chain dehydrogenase/reductase retSDR2 " (SEQ ID No:99)
(xxxiii) "Stromal cell-derived factor 2-like 1 " (SEQ ID No:100)
5 (xxxiv) "Thioredoxin domain-containing protein" (SEQ ID No:101), and
(xxxv) "Voltage-dependent anion channel 1" (SEQ ID No:102),

and wherein the one or more proteins of the Nicastrin (b) complex are selected
from the group consisting of of

- 10 (i) "18 kDa microsomal signal peptidase subunit" (SEQ ID No:53)
(ii) "25 kDa microsomal signal peptidase subunit" (SEQ ID No:119)
(iii) "ATP-binding cassette, sub-family A, member 3" (SEQ ID No:103)
(iv) "Aph-1a" (SEQ ID No:1)
15 (v) "BACE1" (SEQ ID No:38)
(vi) "BSCv protein (FRAGMENT)" (SEQ ID No:70)
(vii) "CAMK4" (SEQ ID No:104)
(viii) "CGI-13" (SEQ ID No:72)
(ix) "Casein kinase II beta chain" (SEQ ID No:74)
20 (x) "Cathepsin B" (SEQ ID No:75)
(xi) "DCTN1" (SEQ ID No:106)
(xii) "ENSG00000144840" (SEQ ID No:79)
(xiii) "FACL3" (SEQ ID No:108)
(xiv) "FACL4" (SEQ ID No:109)
25 (xv) "FLJ13977" (SEQ ID No:81)
(xvi) "FLJ20342" (SEQ ID No:56)
(xvii) "FLJ20481" (SEQ ID No:82)
(xiii) "FLJ22390" (SEQ ID No:84)
(xix) "ICAM-2" (SEQ ID No:87)
30 (xx) "KIAA0095" (SEQ ID No:110)
(xxi) "KIAA0922" (SEQ ID No:111)
(xxii) "KIAA1181 (FRAGMENT)" (SEQ ID No:88)
(xxiii) "KIAA1533 (FRAGMENT)" (SEQ ID No:89)

- (xxiv) "Mesenchymal stem cell protein DSCD75" (SEQ ID No:91)
(xxv) "NICE-3" (SEQ ID No:58)
5 (xxvi) "Neurotrypsin" (SEQ ID No:92)
(xxvii) "Nicastrin" (SEQ ID No:9)
(xxiii) "PAS domain containing serine/threonine kinase" (SEQ ID No:112)
(xxix) "PP1, regulatory subunit 15B" (SEQ ID No:93)
(xxx) "Pen-2" (SEQ ID No:10)
10 (xxxi) "Presenilin-1" (SEQ ID No:14)
(xxxii) "Presenilin-2" (SEQ ID No:66)
(xxxiii) "Protein amplified in osteosarcoma (OS-9)" (SEQ ID No:94)
(xxxiv) "Protein similar to stromal cell-derived factor 2" (SEQ ID No:95)
(xxxv) "Protocadherin beta 8" (SEQ ID No:96)
15 (xxxvi) "REP8 protein" (SEQ ID No:97)
(xxxvii) "RING finger protein 5" (SEQ ID No:98)
(xxxiii) "Retinal short-chain dehydrogenase/reductase retSDR2" (SEQ ID No:99)
(xxxix) "Stromal cell-derived factor 2-like 1" (SEQ ID No:100)
(xl) "Thioredoxin domain-containing protein" (SEQ ID No:101)
20 (xli) "homolog of yeast golgi membrane protein yif1p (yip1p-interacting factor)"
(SEQ ID No:113), and
(xlii) "tyrosine phosphatase ensg00000149185" (SEQ ID No:86),

and wherein the one or more proteins of the Nicastrin (c) complex are selected from
25 the group consisting of

- (i) "APP-C99" (SEQ ID No:120)
(ii) "Nicastrin" (SEQ ID No:9)
(iii) "Psen1" (SEQ ID No:3)
30 (iv) "aph-1a" (SEQ ID No:1)
(v) "APP" (SEQ ID No:23)
(vi) "CtnnA1" (SEQ ID No:47)
(vii) "CtnnA2" (SEQ ID No:48)

- (viii) "CtnnB1" (SEQ ID No:46)
(ix) "CtnnD1" (SEQ ID No:49)
5 (x) "JUP" (SEQ ID No:2)
(xi) "NCadh" (SEQ ID No:50)
(xii) "ACAT1" (SEQ ID No:4)
(xiii) "CGI-13" (SEQ ID No:72)
(xiv) "CK2B" (SEQ ID No:59)
10 (xv) "CLGN" (SEQ ID No:54)
(xvi) "ECSIT" (SEQ ID No:55)
(xvii) "FACL3" (SEQ ID No:11)
(xiii) "FLJ20481" (SEQ ID No:82)
(xix) "ITM2C" (SEQ ID No:13)
15 (xx) "ITPR1" (SEQ ID No:16)
(xxi) "KIAA0363" (SEQ ID No:105)
(xxii) "MDR1" (SEQ ID No:18)
(xxiii) "Neurotrypsin" (SEQ ID No:19)
(xxiv) "PTP LOC114971" (SEQ ID No:60)
20 (xxv) "RetSDR2" (SEQ ID No:21)
(xxvi) "SFXN1" (SEQ ID No:24)
(xxvii) "SPC18" (SEQ ID No:26)
(xxiii) "SPC22" (SEQ ID No:27)
(xxix) "SPC25" (SEQ ID No:28)
25 (xxx) "SPTLC2" (SEQ ID No:117)
(xxxi) "stearoyl-CoA desaturase" (SEQ ID No:29)
(xxxii) "STT3" (SEQ ID No:61)
(xxxiii) "TMP21" (SEQ ID No:30)
(xxxiv) "UGCGL1" (SEQ ID No:45)
30 (xxxv) "visinin-like 1" (SEQ ID No:37)
(xxxvi) "Wolframin" (SEQ ID No:67)
(xxxvii) "YME1L1" (SEQ ID No:32)

and wherein the one or more proteins of BACE1 (a) complex are selected from the group consisting of

- (i) "CGI-13" (SEQ ID No:72)
- (ii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:35)
- (iii) "Calsyntenin 1" (SEQ ID No:36)
- (iv) "Delta-like homolog" (SEQ ID No:118)
- (v) "FLJ30668" (SEQ ID No:69)
- (vi) "FLJ39249" (SEQ ID No:71)
- (vii) "ITCH" (SEQ ID No:73)
- (viii) "KIAA1250" (SEQ ID No:107)
- (ix) "Nicastrin" (SEQ ID No:9)
- (x) "Nogo-A" (SEQ ID No:77)
- (xi) "PDGFRB" (SEQ ID No:78)
- (xii) "PTK7" (SEQ ID No:80)
- (xiii) "SERPINA1" (SEQ ID No:83)
- (xiv) "SIM TO Y71H10A. 2.P" (SEQ ID No:85)
- (xv) "STX10" (SEQ ID No:65)
- (xvi) "Sortilin-related receptor" (SEQ ID No:52)
- (xvii) "Thioredoxin domain-containing protein" (SEQ ID No:101)
- (xviii) "integral membrane transporter protein" (SEQ ID No:114)
- (xix) "kinectin 1 (kinesin receptor)" (SEQ ID No:90), and
- (xx) "BACE1" (SEQ ID No:38),

and wherein the one or more proteins of the BACE1 (b) complex are selected from the group consisting of

- (i) "APP" (SEQ ID No:23)
- (ii) "Nicastrin" (SEQ ID No:9)
- (iii) "ACAT1" (SEQ ID No:4)
- (iv) "APLP2" (SEQ ID No:22)
- (v) "BRI" (SEQ ID No:5)

- (vi) "calsyntenin 1 " (SEQ ID No:6)
(vii) "CELSR2" (SEQ ID No:39)
(viii) "CGI-13 " (SEQ ID No:72)
5 (ix) "DLK1" (SEQ ID No:7)
(x) "DSCD75" (SEQ ID No:8)
(ii) "FADS2" (SEQ ID No:40)
(xii) "GPR49" (SEQ ID No:115)
(xiii) "ITM2C" (SEQ ID No:13)
10 (xiv) "KiDins220" (SEQ ID No:17)
(xv) "LAPTM4B " (SEQ ID No:33)
(xvi) "Neurotrypsin" (SEQ ID No:19)
(xvii) "NogoA" (SEQ ID No:41)
(xviii) "OS-9" (SEQ ID No:42)
15 (xix) "PDGFRB" (SEQ ID No:43)
(xx) "PTK7 " (SEQ ID No:44)
(xxi) "RetSDR2" (SEQ ID No:21)
(xxii) "S100alpha" (SEQ ID No:34)
(xxiii) "SORL1" (SEQ ID No:25)
20 (xxiv) "stearoyl-CoA desaturase" (SEQ ID No:29)
(xxv) "TMP21" (SEQ ID No:30)
(xxvi) "UGCGL1" (SEQ ID No:45)
(xxvii) "BACE1" (SEQ ID No:38)

25 and wherein the one or more proteins of the Psen2-complex are selected from the group consisting of

- (i) "aph-1a" (SEQ ID No:1)
(ii) "Nicastrin" (SEQ ID No:9)
30 (iii) "CGI-13 " (SEQ ID No:72)
(iv) "DSCD75" (SEQ ID No:8)
(v) "ECSIT" (SEQ ID No:55)
(vi) "FACL3" (SEQ ID No:11)

- (vii) "FADS2" (SEQ ID No:40)
(viii) "FLJ10579" (SEQ ID No:12)
5 (ix) "FLJ20481" (SEQ ID No:82)
(x) "ITPR1" (SEQ ID No:16)
(xi) "KIAA0090" (SEQ ID No:57)
(xii) "MDR1" (SEQ ID No:18)
(xiii) "NicAChRa3" (SEQ ID No:62)
10 (xiv) "PLD3" (SEQ ID No:20)
(xv) "SFXN1" (SEQ ID No:24)
(xvi) "SLC4A2" (SEQ ID No:63)
(xvii) "SORT1" (SEQ ID No:15)
(xvii) "SPC18" (SEQ ID No:26)
15 (xix) "SPC22" (SEQ ID No:27)
(xx) "SPC25" (SEQ ID No:28)
(xxi) "SPTLC2" (SEQ ID No:117)
(xxii) "stearoyl-CoA desaturase" (SEQ ID No:29)
(xxiii) "STT3" (SEQ ID No:61)
20 (xxiv) "TMP21" (SEQ ID No:30)
(xxv) "VLCAD" (SEQ ID No:31)
(xxvi) "Wolframin" (SEQ ID No:67)
(xxvii) "YME1L1" (SEQ ID No:32), and
(xxvii) "Psen2" (SEQ ID No:121)

25 and wherein the at least one protein of PTK7 complex is selected from the group consisting of .

- (i) "APP" (SEQ ID No:23)
30 (ii) "BRI" (SEQ ID No:5)
(iii) "CELSR2" (SEQ ID No:39)
(iv) "DLK1" (SEQ ID No:7)
(v) "FADS2" (SEQ ID No:40)

(vi) "HIFPH3/EGLN3 " (SEQ ID No:64)

(vii) "ITM2C" (SEQ ID No:13)

(viii) "Nap1-like " (SEQ ID No:116)

(ix) "Reelin" (SEQ ID No:51)

(x) "PTK7" (SEQ ID No:44)

14. The complex of any of claims 12 or 13, wherein one or more of the proteins are present in the form a fusion protein comprising said protein fused to an amino acid sequence different from that of the protein.

15. The complex of claim 14, wherein said amino acid sequence is an affinity tag or label.

16. A process for preparing and optionally analyzing a complex of any of claims 12 to 15 or of one or more components thereof comprising the following steps:

Expressing a protein of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the protein, preferably a tagged protein, and optionally disassociating the protein complex and isolating the individual complex members.

17. The process according to claim 16, wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

18. The process according to any of claims 16 or 17, wherein the two tags are separated by a cleavage site for a protease.

19. Nucleic acid construct containing one or more nucleic acids encoding proteins of a complex according to any of claims 12 to 15.

20. Host cell, containing a nucleic acid construct according to claim 19.

- 5 21. A kit comprising in one container the complex of any of claims 12 to 15, optionally together with an antibody against the complex and/or further components such as reagents and working instructions.
- 10 22. The kit according to claim 13 for processing a substrate of a complex of any one of claims 12 to 15.
23. The kit according to any of claims 21 or 22 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
- 15 24. Array in which at least a complex according to any of claims 12 to 15 is attached to a solid carrier.
- 20 25. A process for processing a substrate of a complex of any one of claims 12 to 15 comprising the step of bringing into contact a complex to any of claims 12 to 15 with said substrate, such that said substrate is processed.
- 25 26. A pharmaceutical composition comprising the protein complex of any of claims 12 to 15.
27. The pharmaceutical composition according to claim 26 for the treatment of neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
- 30 28. A method for screening for a molecule that binds to the complex of any one of claims 12 to 15, comprising the following steps:
(a) exposing said complex, or a cell or organism containing said complex, to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex.

5 29. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of claims 1 to 7 comprising the steps of:

(a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and

10 (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex.

30. The method of claim 29, further comprising the step of determining whether said candidate molecule modulates gamma secretase and/or beta secretase activity.

15

31. The method of any of claims 29 or 30, wherein the amount of said complex is determined.

20 32. The method of any of claims 29 or 30, wherein the activity of said complex is determined.

25 33. The method of claim 32, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

30

34. The method of claim 33, wherein the substrate is APP and the cleavage of APP is analyzed.

35. The method of any of claims 29 or 30, wherein the amount of the individual protein components of said complex are determined.

5 36. The method of claim 35, wherein said determining step comprises determining whether any of the proteins of the respective complex as defined in claim 13 is present in the complex.

10 37. The method of any of claims. 29 to 36, wherein said method is a method of screening for a drug for treatment or prevention of neurodegenerative disease such as Alzheimer's disease.

15 38. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of claims 1 to 7 for the manufacture of a medicament for the treatment or prevention of a neurodegenerative disease such as Alzheimer's disease.

20 39. The use according to claim 38, wherein the modulating molecule is a FADS2 interacting molecule, preferably a FADS2 inhibitor.

40. The use according to claim 39, with the features as defined in claims 2 to 6.

25 41. A method for the production of a pharmaceutical composition comprising carrying out the method of any of claims 28 to 37 and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

30 42. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, component disposition of, or intracellular localization of the complex of any one of claims 12 to 15; comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex.

43. The method of claim 42, wherein the activity of gamma secretase and/or beta secretase is determined.

44. The method of any of claims 42 or 43, wherein the amount of said complex is determined.

45. The method of any claim 42 or 43, wherein the activity of said complex is determined.

46. The method of claim 45, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

47. The method of any of claims 42 or 43, wherein the amount of the individual protein components of said complex are determined.

48. The method of claim 47, wherein said determining step comprises determining whether any of the proteins according to claim 13 is present in the complex.

49. The complex of any one of claims 12 to 15, for use in a method of diagnosing a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

50. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of any one of claims 12 to 15, comprising administering to a subject in need of such treatment or prevention a therapeutically

effective amount of one or more molecules that modulate the amount of, activity or, or protein components of, said complex.

- 5
51. The method according to claim 50, wherein the modulating molecule is a FADS2 interacting molecule, preferably a FADS2-inhibitor.
- 10
52. The method according to claim 51, with the features as defined in any of claims 2 to 6.
53. The method according to any of claims 50 to 52, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.
- 15
54. The method according to any of claims 50 to 53, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
- 20
55. The complex of any of claims 12 to 15 as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
- 25
56. Use of a FADS2 interacting molecule for the modulation of beta secretase and/or gamma secretase activity in vitro.